Remarks

Status of the Claims

Claims 1-3, 23 and 24 are pending in the present application. Applicants add new claims 25-27 and amend claims 1-3 and 23. Support for amended claim 1 is found in the specification at least, for example, at page 9, lines 18-21 and in Figure 1D. Support for amended claim 2 and new claim 25 is found at least, for example, at page 9, lines 11-14, and in Figure 1B. Support for amended claim 3 and new claims 26 and 27 is found at least, for example, at page 9, lines 15-18, and in Figure 1C. Support for amended claim 23 is found at least, for example, in Example 2. Accordingly, upon entry of these amendments, claims 1-3 and 23-27 will be pending and presented for consideration.

Interview

Applicants thank Examiner Mertz for the interview on March 16, 2004, when proposed amendments to the claims pending in this application were discussed. Applicants have amended the claims accordingly and submit that the claims are presently in condition for allowance.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-3 and 23 are rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,457,038 to Trinchieri *et al.* ("Trinchieri") in view of International Publication No. WO 97/20062 to Steele *et al.* ("Steele"). Applicants respectfully traverse this rejection.

Reasonable Expectation of Success

Claims 1-3 and 24-27 are drawn to immunoglobulin (Ig)–IL-12 fusion proteins. Claim 23 is drawn to a method of increasing the circulating half-life of IL-12 by linking the p35 subunit of IL-12 to a peptide. Based on obstacles specific to the expression and purification of a bioactive fusion protein with a heterodimeric cytokine generally and with IL-12 in particular, Trinchieri and Steele do not provide any reasonable expectation of successfully generating fusion proteins of the claimed invention.

Degradation and secretion of the p35 subunit of IL-12

Trinchieri and Steele fail to provide any expectation of successfully preventing intracellular degradation of the p35 subunit of IL-12 fusion protein. Protein expression studies using IL-12 fusion protein and individually expressed subunits of IL-12 demonstrated that the p35 subunit of IL-12 cannot be secreted from the cell, even when expressed as a fusion protein with an Ig Fc fragment (page 14, lines 15-18; and Figure 2, lane 1 in the present application). As a result, excess p35 is likely degraded in the endoplasmic reticulum, which in turn, is likely to have deleterious effects on the host cell (page 15, lines 5-7 in the present application).

These studies also showed, however, that the p35 subunit was secreted from the cell only when paired with a p40 subunit co-expressed in the same cell (page 14, lines 19 and 20 in the present application). In particular, p35 can be secreted either as an Fc-p35 fusion paired with an Fc-p40 fusion, an Fc-p35 fusion paired with free p40 protein, or as free p35 paired with Fc-p40 fusion protein (see Figure 2, lanes 3, 4, and 5, respectively; and page 14, lines 19-22 in the present application). Based on these studies, Applicants have determined how to secrete p35, avoiding its intracellular degradation. The problem of p35 degradation is not addressed by Trinchieri and Steel as they provide no expectation of successfully overcoming this obstacle.

Bioactivity of IL-12 fusion protein

Trinchieri and Steele fail to provide any expectation of success that the fusion proteins of the claimed invention would possess IL-12 bioactivity. Applicants are not aware that any heterodimeric cytokine had ever been successfully synthesized and secreted in a bioactive form as a fusion protein with an Ig heavy chain prior to the instant invention. To be active, the fusion protein must permit heterodimerization of the p35 and p40 subunits and binding to and activation of an IL-12 receptor. The cited references fail to provide the requisite expectation that an IL-12 fusion protein with an Ig heavy chain portion could simultaneously achieve all of these requirements.

Applicants have shown for the first time that the IL-12 molecule in the claimed fusion proteins is biologically active. For example, IL-12 fusion proteins were shown to stimulate

interferon-γ production (see, *e.g.*, page 17, lines 3-7; page 21, lines 11-15; Figure 4; and Figure 5, panels C and D in the present application). In another study, IL-12 fusion protein was shown to stimulate proliferation of mitogen-activated human peripheral blood monocytes (see, *e.g.*, page 21, lines 7-9; and Figure 5, panel B in the present application). By properly inducing cellular responses that are normally induced by endogenous IL-12, the claimed fusion proteins include bioactive IL-12. Since Trinchieri and Steele do not teach IL-12 fusion proteins, these references do not address or solve the problem of maintaining IL-12 bioactivity in a fusion protein. Therefore, Trinchieri and Steele could not provide any expectation that the claimed fusion proteins would possess IL-12 bioactivity.

IL-12 bioactivity could be impaired by contamination with Fc-p40 homodimer, which inhibits the IL-12 receptor (see Steele). Co-expression of p40 fusion protein and p35 (either alone or as a fusion protein) could result in secretion of a mixture of p35-p40 heterodimeric and p40 homodimeric fusion proteins (see page 15, lines 3-5; and Figure 3 in the present application). Even in combination, Steel and Trinchieri do not address this further obstacle to synthesis of a fusion protein that is an IL-12 receptor agonist.

Proposed Modification is Unsatisfactory for Intended Purpose

The proposed modification of the Steele fusion protein would render it unsatisfactory for its intended purpose. The p40-Ig fusion protein of Steele is intended to bind to and to competitively inhibit the IL-12 receptor (see Steele, page 1, lines 20, 21, 32 and 33). The function of this inhibitor is dependent on the absence of the p35 subunit, which, when present, activates the IL-12 receptor by initiating signal transduction (see Steele, page 1, lines 19-25; and page 1, line 32 to page 2, line 2). Therefore, modifying the fusion protein of Steele to include a p35 subunit would render the inhibitor unsatisfactory for its intended purpose, which is to prevent IL-12 receptor activation.

Based on each of the foregoing arguments, even in combination, Trinchieri and Steele could not render obvious the inventions of claims 1-3, 23 and 24. Accordingly, Applicants

respectfully request that the rejection of the pending claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

Claims 1-3 and 23-27 are pending and believed to be in condition for allowance. Examiner Mertz is invited to telephone the undersigned attorney to discuss any remaining issues.

Respectfully submitted,

Date: April 14, 2004
Reg. No. 41,640

Michael H. Brodowski
for Brian A. Fairchild
Attorney for Applicant(s)
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

Tel. No.: (617) 248-7012
Fax No.: (617) 248-7100

3048903